ORIGINAL ARTICLE

Drug-induced prolongation of the QT interval: regulatory dilemmas and implications for approval and labelling of a new chemical entity

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INTRODUCTION

QT interval of the electrocardiogram (ECG) reflects the duration of the ventricular action potential. It is prolonged usually when there is delayed repolarisation due to diminished outward potassium current during phase 2 and 3 of the action potential. Clinically, it is an important pharmacological effect of a drug. This effect, when exerted in a carefully controlled manner, is the primary pharmacological mechanism by which class III anti-arrhythmic drugs exert their beneficial effect. However, QT interval prolongation, when excessive, can be pro-arrhythmic and can degenerate into torsade de pointes (TdP), a unique polymorphic form of ventricular tachycardia [1]. Apart from clinical manifestations resulting from impaired circulation, TdP is potentially fatal. TdP subsequently degenerates into ventricular fibrillation in about 20% of cases [2] and, not uncommonly, cardiac arrest and sudden death may be the outcome [3]. The overall mortality is of the order of 10–17% [2,4]. Drug-induced prolongation of QT interval is therefore a highly undesirable pharmacological effect as far as non-antiarrhythmic drugs are concerned. A number of antianginal drugs as well as non-cardiovascular drugs have been shown to carry this concentration-related liability. There are now well over 10 antianginal and 80 noncardiac drugs, which have been reported to significantly prolong the QT interval and/or induce TdP.

It is recognised that QT interval prolongation *per se* is not necessarily harmful. However, when excessive, it can degenerate into TdP and the risk of induction of TdP bears an exponential relationship to the degree of prolongation. The link between QT interval prolongation and TdP is complex and influenced by many other factors. Not all the drugs prolonging the QT interval, or blocking the outward repolarising potassium current, to the same extent carry the same torsadogenic risk. Drugs such as amiodarone and racemic sotalol prolong the QT interval but their torsadogenic potential is nowhere near as high as one might anticipate. Other ancillary pharmacological properties of these drugs no doubt modulate their torsadogenic risk. Myxoedema is also associated with prolongation of QT interval but this is not a disease that one typically associates with TdP. Notwithstanding, QT interval is the best surrogate marker we currently have for TdP and TdP is, by definition, associated with and follows concomitant prolongation of the QT interval.

In view of the potentially fatal outcome (even when due to antiarrhythmic drugs), the focus on the effect of drugs on QT interval has shifted dramatically from one of a beneficial antiarrhythmic mechanism to that of a highly undesirable pharmacological activity. Given the wide range of drugs from diverse chemical and pharmacotherapeutic classes that are known to be associated with a potential to prolong the QTc interval, it is important that all new chemical entities (NCEs) are characterised, during preclinical and clinical development, for their effect on cardiac repolarisation. The Committee for Proprietary Medicinal Products (CPMP) of the European Union (EU) adopted two significant documents in December 1997. One of these was the CPMP document 'Points to Consider: The Assessment of the Potential for QT Interval Prolongation by Non-cardiovascular Medicinal Products' [5]. A number of drugs, such as terfenadine, astemizole, pimozide, cisapride and others, have the propensity to prolong the QT interval and induce TdP and other proarrhythmias, more often (but not always) as a result of drug interactions. Therefore, the other significant document was the CPMP 'Note for Guidance on the Investigation of Drug Interactions' [6].

EVALUATION OF RISK

The two documents adopted by the CPMP recommend preclinical and clinical strategies by which EU regulators would like to see an NCE investigated for its potential to induce proarrhythmic prolongation of the QT interval and to give rise to drug interactions, respectively.

Rather than focus on one particular set of data, the results from these strategic set of investigations should be evaluated collectively as well as drawing on experiences with other drugs of the same chemical and/or pharmacotherapeutic classes in order to assess the potential of an NCE to prolong the QT interval during its routine clinical use. The conclusions from this evaluation could have considerable impact for the approvability and/or labelling of the NCE concerned. It is therefore important that this surrogate marker of TdP is carefully and adequately investigated.

The task may appear at first to be relatively straightforward. In reality, even when the potential is investigated adequately, the regulatory assessment of the potential of an NCE to prolong the QTc interval and/or induce TdP during its routine clinical use is complicated by a variety of factors [7]. These include:

1 the validity and applicability of the preclinical data to humans;
2 the limitations of clinical trials;
3 spontaneous variability in QTc interval;
4 defining proarrhythmic thresholds of changes in QTc interval;
5 the role of other ancillary physico-chemical and pharmacological properties of the NCE in modulating its proarrhythmic risk;
6 the rate-correction formula that should be applied to correct the measured QT interval for changes in heart rate (QTc interval) following administration of the NCE;
7 placing the proarrhythmic risk from QTc interval prolongation produced by the NCE against its potential benefits and the risk/benefits of available alternatives.

REGULATORY DILEMMA

The difficulty from a regulatory perspective is to determine whether a change in QTc interval observed in a few individuals following the administration of a drug in clinical trials is drug-induced or simply a spontaneous normal variation. There are risks to an inappropriate conclusion. If the change is a spontaneous one but attributed to a drug, the result is an inappropriate restrictive labelling of the drug, denying effective medicines to potential beneficiaries. On the other hand, if the change is indeed drug-induced but dismissed as simply a spontaneous normal variation, there is the risk of a serious public health hazard.

Preclinical data are often inconclusive when in vivo studies fail to show the effect predicted from in vitro preparations. This has been observed for a number of torsadogenic drugs. The concentrations producing an effect either in vivo or in vitro are often much higher than those attained clinically. The degree of myocardial binding of the drug can be an important link that may explain the discrepancy between in vitro and in vivo findings. Protein binding of the drug prompts one to question whether the focus should be on free fraction of the drug in the plasma when extrapolating from preclinical to clinical setting.

Clinical trials have limited power to detect the proarrhythmic risk. They are efficacy-orientated, patient population randomised is highly selected with numerous exclusion criteria and therefore, in all likelihood, not truly representative of the ultimate target population. In addition, the sample size is relatively small and the studies are not powered to detect low frequency events associated with the NCE *per se* or those that follow drug interactions.

A regulatory decision is therefore heavily influenced by changes in QTc interval observed in a few individuals. Isolated prolongation of the QTc interval may be a common finding in early dose-escalation studies and one of the problems in interpreting data from clinical trials is separating drug-induced effects from spontaneous variability that is observed in QTc intervals within an individual. This variability can be as high as ± 60 ms or more. Furthermore, the QTc interval may be influenced by a number of factors unrelated to drug administration (e.g. posture, respiration, autonomic tone, exercise, stress, food and menstrual cycle) and it also shows a diurnal pattern of variation.

A relationship to the drug is likely if similar changes are not observed in the placebo group and increases in the QTc interval occur frequently, are dose-related and have a time course consistent with drug effect. Availability of in vitro electrophysiological data on the effect of the drug on cardiac action potential duration and ion channels greatly facilitates the regulatory assessment. The two hallmarks of class III activity are concentration-dependence and negative use-dependency. Because almost all drugs prolong the QTc interval by blocking the delayed rectifier potassium channel (I_{Kr}), additional data on the effect of the drug on this channel provides further corroborative evidence.

Evaluation of whether or not the effects observed in vitro are clinically relevant can be further refined by consideration of some additional information, such as the lipophilicity of the drug (or its cardiotoxic metabolite), its distribution ratio between plasma and the myocardial tissue and any other ancillary pharmacological activities of the compound (e.g. sodium or calcium channel or α- or β-adrenoceptor blocking activities). An important parameter in assessing the risk during routine clinical use of the drug might be the ratio of the concentration in the bathing fluid producing a 50% block of the I_{Kr} compared to the plasma concentration required for effecting the receptor targeted for efficacy. This helps to identify risk ratio for many drugs that block I_{Kr} at only high concentrations.

The traditionally used Bazett formula for correction of the measured QT interval for variations in heart rates ($QTc = QT/RR^{0.50}$) has limitations for drugs that significantly increase the heart rate. Although none of the 30 or so formula available is entirely satisfactory, the Fridericia correction ($QTc = QT/RR^{0.33}$), or preferably a study-specific derived formula ($QTc = QT/RR^{x}$), are likely to prove more appropriate but these are difficult to apply, especially in routine clinical practice. They certainly appear to be more appropriate than Bazett's correction on which to base regulatory decisions.

Heterogeneity in study designs and their durations and the doses used, together with a diverse methods of reporting the effect of drugs on mean changes in QTc interval, have made it difficult to assess the significance of mean changes produced by even some of most torsadogenic drugs. While some studies have reported mean change in maximum QTc interval ('peak effect'), others have reported mean change in QTc interval averaged across the dosing interval. Because metabolites may also mediate blockade of potassium channels, it is worth emphasising that the peak effect of interest is the maximum effect on QTc interval and not necessarily the effect at peak concentration of the parent drug.

Mean increases in peak QTc interval were 9 and 22 ms following single oral doses of 10 mg and 50 mg thioridazine, respectively [8] and 23, 19, and 0 ms following single oral doses of 200 mg racemic terodiline, 100 mg R-terodiline and 100 mg S-terodiline, respectively [9]. Single oral doses of moxifloxacin increased the mean peak QTc interval by 15 ms on 400 mg dose and by 17 ms on 800 mg dose, both relative to placebo [10]. This compares with sparfloxacin-induced increases in the mean peak QTc interval of 15 ms by a single oral dose of 200 mg and of 14 ms by a single oral dose of 400 mg, both relative to placebo [11]. In one study, single oral doses of 6 mg pimozide increased mean peak QTc interval by 13.3 ms [12] while another study reported that mean (± SD) daily doses of 10.68 (± 7.22) mg pimozide for 9 weeks increased the mean QTc interval by 24 ms, there being no relationship to dose or age of the patients [13]. Mean peak increases of 10, 16, 29, 51 and 60 ms in QTc interval were seen following single oral doses of 200 mg, 400 mg, 800 mg 1200 mg and 1600 mg of sparfloxacin to healthy volunteers [14,15]. These compare with a steady state increase in mean QTc interval of 11 ms following 200 mg sparfloxacin in 813 Phase III patients [16]. Cisapride 20 mg twice a day for 7 days increased the mean peak QTc interval by 6.8 ms at 1.5 h and 10.9 ms at 3 h postdose (AstraZeneca; pers. comm.). The mean increase in QTc interval (peak or average not specified) was 6 ms following administration of 10 mg astemizole for 2 weeks. The mean increase in peak QTc interval at steady state was reported to be 21 ms following 12–24 mg and 31 ms following the highest dose of

24 mg of sertindole. The difficulties in interpreting such heterogeneous data on mean changes from baseline when comparing or evaluating drugs are immediately apparent. Based on these and other data on non-torsadogenic drugs, the likely prognostic significance of the placebo-corrected mean peak effects on QTc interval, computed by the author, is shown in *Table I*.

While mean changes in peak effect from baseline may raise a suspicious signal, it is the outliers with the categorical responses that provide the most valuable information of regulatory interest on the potential of a drug to prolong the QT interval and induce TdP. Apparently small mean changes may easily conceal large changes in individuals of specific regulatory interest. Small, apparently insignificant, increases in the QT interval also occur in many patients taking an offending drug but in only a few susceptible patients (generally the ones excluded from clinical trials) are these changes marked enough to lead to induction of ventricular tachycardias. So, what categorical responses are considered to be predictive of risk?

From the observed placebo variability in a double-blind, four-period crossover, dose escalation, study on terfenadine and which involved 28 normal healthy volunteers and 28 patients with stable cardiovascular disease [17], it was calculated that an increase in (Bazett corrected) QTc of 35 ms while receiving drug therapy is likely to represent a drug effect at the 95% confidence interval. It was also calculated that the probability of a 50 ms increase being of chance origin was 0.0003 over 1 day and 0.002 over 6 days.

From data on QTc intervals of cases of TdP on a variety of cardiac and noncardiac drugs [18–20], it is evident that a QTc interval of > 500 ms while receiving the offending drug carries a serious risk of induction of TdP. The border between antiarrhythmic and proarrhythmic prolongations of QT interval is neither sharp nor well-defined, but there is now persuasive evidence that a prolongation of QT interval, corrected for heart rate, above 500 ms carries undue risks of TdP, particularly when associated with slow heart rates.

Table I Likely prognostic significance of the effect of 1 × clinical dose on mean maximum or peak placebo-corrected QTc interval in man.

Mean maximum or peak placebo-corrected increase in QTc interval	Likely potential torsadogenic risk
≤ 5 ms	None
6–10 ms	Unlikely
11–15 ms	Possible
16–20 ms	Probable
21–25 ms	Almost definite
≥ 26 ms	Definite

Therefore, regulatory assessment of risk is heavily influenced by the number of individuals showing categorical responses to an NCE in comparison with placebo and/or comparators. Available data also suggest that in individual subjects an increase of 60 ms in peak or maximum QTc interval over baseline or a postdose QTc interval of 500 ms or more (irrespective of the increase from baseline) is highly predictive of the potential risk. Such 'outliers' analysis is expected to be included in any regulatory submission. Although the mean change in QTc interval produced by sparfloxacin in 813 patients amounted to 11 ms (+ 2.9%), it had exceeded 500 ms in 10 of these 813 patients [16].

EVALUATION OF APPROVABILITY AND LABELLING IMPLICATIONS

Once it is concluded that the drug is likely to significantly prolong the QTc interval at clinically relevant concentrations, the approval of the drug depends very much on the potency and the frequency of the QTc prolongation by the drug, the likelihood of this degenerating into TdP, the susceptibility of the target population, overall safety profile of the drug, its therapeutic indication and the level of efficacy (therapeutic benefit). Availability of alternatives with superior risk/benefit ratio is an important determinant of the approvability of the drug concerned.

Despite prolonging the QTc interval, it is not inconceivable that drugs with a potential to prolong QTc interval may be approved provided a carefully planned clinical development programme has identified a population in whom the benefits of the drug can be shown to outweigh the small potential risk of proarrhythmias or the drug can be shown to fulfil an unmet need. For such drugs, the prescribing information would require careful crafting of the indication to reflect the population and the disease entity most likely to benefit as well as detailed information ('labelling') on the proarrhythmic risk with carefully selected dose regimen and appropriate contraindications, description of interactions and special precautions and monitoring requirements during their clinical use. In what follows, the kind of restrictions and requirements that are typically applied will be exemplified by the UK, EU and/or the US labelling of a few torsadogenic drugs.

LABELLING RESTRICTIONS

Indication and posology

Reflecting the robust data on efficacy, restriction of an indication may be one way of restricting the population likely to be exposed to the NCE. If the NCE has any special advantages over the available alternatives, only those who are intolerant of these alternatives may be considered the most appropriate target population. Apart from this restriction with regard to target population, further restriction may be placed by characterising the disease to be treated by the NCE.

Allied to the indication is the posology of the NCE. The posology section may be required to include information on maximum single dose, maximum daily dose, duration of therapy, starting dose and, depending on the half-life of the drug and the time required to reach steady state, a shallow dose titration schedule.

The most recent example of restriction of indications is thioridazine. From July 2000, the indication for thioridazine in the USA was amended by the Food and Drug Administration (FDA) to state:

> thioridazine is now indicated *only* for schizophrenic patients who fail to show an acceptable response to adequate courses of treatment with other antipsychotic drugs, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects. Thioridazine has not been systematically evaluated in controlled trials in treatment refractory schizophrenic patients and its efficacy in such patients is unknown.

In view of its long half-life (55 h but may be as high as 150 h in some), the dose schedule of pimozide was revised to recommended a starting dose of 20 mg daily with a maximum daily dose of 60 mg. Following reports of TdP and other ventricular arrhythmias, the dose schedule of pimozide was re-amended to recommend an initial starting dose of 2–4 mg daily (exceptionally 10 mg in acute schizophrenia, but even this recommendation was subsequently removed). The dose was to be increased by a shallow dose titration ('dose increases should be made at weekly intervals or longer, and by increments of 2–4 mg in the daily dose'). The maximum daily dose reduced from 60 mg to 16–20 mg.

Contraindications

The labeling section most likely to be effective in containing the clinical risk, if the prescribing physicians adhere to it, is the contraindications. In view of the many pharmacological properties commonly shared by these QT prolonging drugs and the common features associated with drug-induced TdP, it is not surprising that a standard set of contraindications have evolved over time. These include those related to the pharmacokinetics of the drug (comedication with inhibitors of metabolism and patients with hepatic and/or renal dysfunction) and those related to its pharmacodynamics (predisposition to hypokalaemia, bradycardia, cardiac disease and/or arrhythmias, pre-existing prolongation of QT interval and comedication with other QT prolonging drugs).

Examples are numerous and include terfenadine, astemizole, cisapride and sertindole. Specific contraindications may also be applied to suit particular drugs. For example, since thioridazine is metabolised by CYP2D6, it was determined that 'thioridazine is also contraindicated in patients known to have reduced levels of cytochrome P450 2D6.' Sertindole too is metabolised by CYP2D6 but in poor metabolisers (PMs) of CYP2D6, an alternative pathway of elimination is that mediated by CYP3A4. Because PMs of CYP2D6 may not be easily identified in routine clinical practice, it was considered essential that sertindole was contraindicated with inhibitors of CYP3A4 generally in order specifically to protect the PMs.

Cisapride is indicated for the relief of symptoms of impaired gastric motility secondary to disturbed and delayed gastric emptying associated with diabetes, systemic sclerosis and autonomic neuropathy. However, because many patients with diabetic or autonomic neuropathy have prolongation of QT interval and greater QTc dispersion, the predisposition of the target population to proarrhythmias is well illustrated by this drug that had to be withdrawn from the market.

Special warnings and precautions for use

Special warnings and precautions may be required with regard to the use of the NCE in special populations such as those with cardiac disease, who are elderly or in receipt of diuretics and other relevant drug classes. Statements may also be required on special monitoring requirements. These may include ECG recordings pretreatment and periodically while the patient is on treatment, in those who exceed specific dose or who develop specific symptoms. Finally, there may be a requirement for including guidance on the circumstances that may warrant the treatment with the NCE to be discontinued.

Pimozide, once again, illustrates the case well. There are detailed statements on proarrhythmias and requirements for a baseline ECG in all patients. Repeat ECG is recommended annually or earlier if clinically indicated. There is also a requirement for periodic assessment of cardiac function in those receiving a daily dose greater than 16 mg. It is advised to review the need for therapy with pimozide if repolarisation changes or arrhythmias are noted. Prior to its suspension, this section of sertindole labelling described data on frequency of QT-related changes observed during clinical trials and included recommendations on baseline and periodic ECGs. This was followed by advice that the treatment with sertindole should be discontinued if QTc interval exceeded 520 ms. The US labelling of thioridazine also requires serum potassium levels to be measured and normalized before starting treatment. It is also recommended that patients with a QTc interval greater than 450 ms should not receive thioridazine and that periodic ECGs and serum potassium levels during thioridazine treatment may be useful and thioridazine should be discontinued in patients who are found to have a QTc interval over 500 ms.

Interactions

In the interactions section of the labelling, whereas the focus at one time was on pharmacokinetic drug interactions, it now also includes details on probable pharmacodynamic interactions. In view of the large number of drugs that prolong the QT interval or predispose a patient to prolongation of the QT interval, this is especially important. Risks of pharmacokinetic and pharmacodynamic interactions from in vivo studies and those predicted to occur from in vitro studies are required to be included. Statements may also be required on the magnitude and duration of these interactions.

The interaction section of pimozide, for example, describes pharmacodynamic interactions associated with comedications such as neuroleptics, risks of diuretic therapy, drugs that prolong the QT interval, drugs with arrhythmogenic potential (antidepressants, antiarrhythmics), its CYP3A4- and CYP2D6-mediated metabolic profile (including in vitro data) and the consequences of the concurrent use of the inhibitors of its metabolism. The labelling of sertindole includes an elaborate drug interactions section that describes its metabolism by CYP2D6 and CYP3A4 and the probable interactions at these loci.

Undesirable effects and overdose

Undesirable effects section should include details of the QTc interval changes and arrhythmias observed in clinical trials and if appropriate, clinical manifestations of these arrhythmias. Statements on the magnitude of the risk, risk factors and course of action in the event of an arrhythmia may also be required if the information is available.

Finally, the overdose section should include information on acute toxicity experience in animals, any observations during clinical trials, dose for proarrhythmic risk, duration of risk, special clinical manifestations, monitoring recommendations, measure to reduce systemic exposure and the role of dialysis.

The overdose section of astemizole included the information on risks of QT prolongation and TdP. It stated that although usually at very high doses, torsade had been reported at doses 2–3 times the recommended dose. It advised monitoring ECG and if the QT interval was prolonged, continue monitoring this as long as it remained prolonged. Half-life of astemizole (1–2 days) and that of desmethylastemizole (9–13 days) were included with a note that haemodialysis did not increase clearance. For overdose with pimozide, it is also recommended to continue monitoring the ECG until it returns to normal and because of its long half-life, it is further advised that patients who have taken an overdose should be observed for at least 4 days. For sertindole, the overdose section included the information that patients taking estimated dosages up to 240 mg had recovered without sequelae and that:

> 'In general, reported signs and symptoms of overdose were … hypotension and transient prolongation of the QT interval. If antiarrhythmic therapy is administered, agents such as quinidine, disopyramide and procainamide carry a theoretical hazard of QT interval prolonging effects that might be additive to those of sertindole'.

INTER-REGIONAL DIFFERENCES

It is worth bearing in mind that, arising from differences in local medical practices and expectations on the risk/benefit of an NCE, and probably because of alternatives available, there are legitimate regional differences on approvability of an NCE that prolongs the QTc interval. These differences exist not only between the USA and the EU but also within the Member States of the EU. Pimozide is approved for schizophrenia in the UK but not by the FDA in the USA, where it is approved only for Gilles de la Tourette syndrome under orphan drug legislation. This significant discrepancy was largely the result of sudden deaths of two patients during acute titration of pimozide to 70–80 mg daily doses during clinical trials investigating the use of pimozide in schizophrenia in the USA.

Consequently, the schizophrenia trials had to be suspended in the USA in 1981.

Other more recent examples of differences in perception of risk/benefit of drugs that were found to prolong the QTc interval during clinical trials are rejection of sertindole in 1996 by Sweden and France although it was approved by all other Member States of the EU and deemed approvable by the FDA and rejection of moxifloxacin by the UK, Belgium, France and the Netherlands during the first filing in 1999 (Belgium and France approved the drug later during a second filing) despite it being approved by the FDA and other Member States of the EU. A more noticeable difference in perception of risk/benefit was the recent rejection of ziprasidone by almost all the Member States of the EU although it was approved by Sweden and the US FDA in 2000. The main QT-related differences between the Swedish the FDA labels for oral ziprasidone when first approved in 2000 are summarised in *Table II*. Following further restrictions to the Swedish labelling, ziprasidone was recently approved in December 2001 by 7 of the other 14 Member States of the EU. Most recently, gatifloxacin (a fluoroquinolone approved in the US in December 1999) was approved by some and not by other Member States in April 2002.

The regional differences are fewer when it comes to withdrawing a drug that has proved to be torsadogenic during its clinical use. In part, this may be due to the fact that the marketing authorisation holders usually withdraw the drug throughout all the markets of the world in one move. Examples are drugs such as astemizole, terodiline, grepafloxacin, cisapride, and droperidol. The only, and the most striking, difference to emerge recently concerns levacetylmethadol ('Orlaam'), approved in the USA in 1994 and in the EU in 1997. Levacetylmethadol is a synthetic opioid analgesic, structurally similar to methadone. The approved indication is for the substitution maintenance treatment of opiate addiction in adults previously treated with methadone, as part of a comprehensive treatment plan including medical, social and psychological care. Following reports of 10 cases of TdP after exposure of about 33 000 patients to the drug worldwide, the CPMP decided to suspend the drug in April 2001 while the FDA were content with strengthening the labelling. In the US, levacetylmethadol drug was relegated to second line therapy in patients who do not show an acceptable response to other adequate treatments for opiate addition (poor efficacy or intolerance) and contraindicated in patients with baseline QTc interval > 430 ms in males and 450 ms in females. ECGs were required 12–14 days after initiation of therapy and periodically thereafter. Other contraindication included any drug known to have the potential to prolong the QT interval.

EFFECTIVENESS OF PRESCRIBING RESTRICTION

An important question in approving the drugs with 'QT liability', albeit with a restrictive labelling, is how effective these prescribing measures are in containing the risk of potentially fatal TdP. Recent experiences with terfenadine and cisapride are not very encouraging [21–23]. It is also questionable whether the patients will be appropriately monitored [24]. In evaluating the risks of a QT prolonging drug during its routine clinical use, it is important to consider whether the prescribing information, however, restrictive, is practical and likely to be adhered to.

SUMMARY

In summary, the effect of an NCE in prolonging the QT interval is seen as a potential hazard to public health. Even the class III antiarrhythmic drugs, which, by definition, exert their therapeutic effect by prolonging the QT interval, are carefully scrutinised for their proarrhythmic safety, given the adverse or neutral outcome on survival associated with drugs such as d-sotalol, dofetilide or azimilide. Because more and more non-antiarrhythmic drugs are now being shown to have the potential to prolong the QT interval, it is important that all NCEs are now thoroughly investigated for this potential early during their preclinical and clinical development. Depending on the strength of the preclinical signal, the data may allow an informed decision to be made early on whether to continue the development of the NCE or to better target its future development. It has been suggested [25] that:

> 'The exclusion of potassium-channel-blocking properties might be considered in the future as a requirement before new molecules are approved for marketing, and more strict warnings in the package inserts of drugs with known repolarization prolonging activity could be enforced.'

In one informal approach by the author to a major multinational pharmaceutical company to ascertain the effect of this strategy on their 'NCE pipeline', it was disclosed that resulting directly from the implementation

Table II Summary of original QT-related labelling and dose of oral ziprasidone in Sweden and the USA.

	Sweden	USA
Indication	In the treatment of schizophrenia	Indicated for the treatment of schizophrenia. When deciding among the alternative treatments available, consider the finding of ziprasidone's greater capacity to prolong the QT/QTc interval compared to several other antipsychotic drugs. Includes an elaboration of the consequences of prolonged QTc interval
Dose schedule	40 mg BD with maximum of 80 mg BD. If indicated, the maximum dose may be reached as early as day 3 of the treatment	20 mg BD adjusted to 80 mg BD. Adjust at intervals of not less than 2 days. Dose greater than 80 mg BD not generally recommended
Contraindications	Known QT prolongation, acute myocardial infarction, or uncompensated heart failure. Arrhythmias treated with class I and class III antiarrhythmic drugs	QT prolonging drugs, known history of QT prolongation, recent myocardial infarction, uncompensated heart failure.
Warnings	Correct electrolyte before ziprasidone treatment. ECG before ziprasidone if patient with stable cardiac disease treated. If symptoms such as palpitation, vertigo, syncope or seizure occur, Possibility of malignant cardiaca rrhythmia should be considered and cardiac evaluation including an ECG should be performed. If QTc > 500 ms, recommended to stop ziprasidone.	10 paragraphs of extensive warnings on QT prolongation and risk of sudden death. Measure and correct electrolyte before treatment. Periodic monitoring of electrolyte if diuretics prescribed during ziprasidone treatment. Discontinue ziprasidone if persistent QTc > 500 ms
Undesirable effects or adverse reactions	Magnitude of QTc changes in clinical trials described, including those with ΔQTc of 30–60 ms	
Overdose	CV monitoring including continuous ECG. No specific antidote.	Immediate CV monitoring including continuous ECG monitoring. If antiarrhythmics administered, disopyramide, procainamide and quinidine carry a theoretical hazard of additive QT prolonging effects that might be additive to those of ziprasidone

of the strategy in the CPMP 'Points to consider' document, 11 NCEs were found, over the 18 month period to November 1999, to have an effect on QT interval – representing an attrition rate of 10%. Of these, eight were dropped from further development and three projects had to be slowed down. None of these compounds was intended to have an effect on ion channels. These 11 were non-cardiovascular as well as cardiovascular drugs, covering a range of therapeutic and chemical classes.

If and when the drug enters clinical evaluation, adequate data will be required on the frequency and the potency of the effect in clinical trials. Any drug-related and clinically significant adverse effect on the QT interval will need to be carefully balanced against the benefits of the NCE (in terms of efficacy and the rest of the safety profile) and the overall risk/benefit of the NCE will require careful comparison to that of the available alternatives.

It should not be assumed that drugs with a potential to prolong QTc interval will never be approved. They may be approved provided a carefully planned clinical development programme has identified a population in whom the benefits of the drug can be shown to outweigh the small potential risk of proarrhythmias or the drug can be shown to confer a unique benefit. Arsenic trioxide illustrates well how even a drug with very marked potential to prolong the QT interval (to > 500 ms in 40% of recipients) and induce TdP may be approved with specific guidelines associated with its clinical use if it is shown to confer a unique benefit. Arsenic trioxide ('Trisenox') was approved in September 2000 in the USA and October 2001 in the EU for its promising efficacy in induction of remission and consolidation in patients with a specific form of acute promyelocytic leukaemia who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy.

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